

CHAPTER 11

Mesolimbic Dopamine and Emotion

A Complex Contribution to a Complex Phenomenon

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Background: The “Anhedonia” Hypothesis of Dopamine Function

For several years, one of the most popular ideas originating from the behavioral neuroscience literature has been that dopamine (DA), particularly in ventral striatum/nucleus accumbens, mediates the “rewarding” effects of positive reinforcers such as food, water, sex, and drugs of abuse. After originating in the animal literature, with a focus on the effects of DA antagonists on operant responding reinforced by food or intracranial self-stimulation (e.g., Wise, 1982), this hypothesis has been extended into virtually every realm of neuroscience (e.g., Peterson, 2005). Moreover, this idea has fully permeated the popular media, including film and the Internet. Years ago it was common to hear the term “pop psychology” used to refer to the popularization of psychological terms in the media. One could argue that the DA hypothesis of “reward” has become a modern-day example of “pop neuroscience,” used to explain our reactions to all pleasurable stimuli, as well as our marketing choices and sexual or political preferences. For example, an Internet search of just one magazine (*The Atlantic*) reveals seven articles in 2012 alone that discuss how DA mediates pleasure or “reward.”

Yet despite its popularity, there are numerous problems with the DA hypothesis of “reward” (sometimes this hypothesis is also referred to as the “anhedonia” hypothesis, because DA antagonists are said to blunt the hedonic impact of reinforcing stimuli; for an overview of the history of this hypothesis, see Wise, 2008). Some of these problems are terminological and conceptual, while others are empirical. Within the field of emotion research, it is probably true that no debate has garnered more interest than the issue of whether positive and negative affect are generated within biologically independent systems (for a review, see Barrett & Bliss-Moreau, 2009). At the center of the argument in favor of the independence view is the claim that dopamine mediates reward, or pleasure. In this chapter we review the theory and evidence challenging the utility of the concept that ventral striatal DA mediates “reward” or hedonia, and point to the rather complex role that mesolimbic DA plays in emotion and motivation.

What Is the Relation between “Reward” and “Hedonia”?

What is “reward”? At the outset, we should state that there is no standard definition or usage of this term, despite the fact that it is so widely employed. Although *reward* can be used as a synonym for *positive reinforcer* when it refers to a stimulus, the term *reward* also has many additional connotations (Cannon & Bseikri, 2004; Salamone, Correa, Farrar, & Mingote, 2007; Salamone & Correa, 2012). Several investigators have noted that usage of this term seems to evoke ideas related to emotion and motivation (White, 1989; Stellar, 2001; Everitt & Robbins, 2005). Initial studies that laid the foundation of the DA hypothesis of “reward” emphasized these emotional processes in suggesting that interference with DA transmission produced “anhedonia” (Wise, 1982; Wise & Raptis, 1985; Wise, Spindler, de Wit, & Gerberg, 1978). The hypothesized “reward” functions of DA have been particularly popular in the drug abuse and self-administration literatures (e.g., Gardner, 1992). More recently, Everitt and Robbins (2005) observed that the use of the term *reward* emphasizes the “subjective, attributional aspects” of reinforcing stimuli. Thus, many researchers use the term *reward* as a thinly veiled synonym for *pleasure* or *hedonia*. Of course, this is not the only usage; *reward* also is used as a synonym for *reinforcement learning*, or as a general term referring to all aspects of appetitive learning, motivation, and emotion. There are three major problems with this: (1) It is virtually impossible to test the hypothesis that DA mediates *reward* when the term can mean so many different things; (2) when used in a very general way (i.e., to describe all processes related in some way to appetitive motivation), *reward* lumps together a number of processes that are easily distinct and dissociable from each other, some of which are mediated by DA, and others that are not; and (3) the idea that *reward* means

“pleasure” is so omnipresent that use of the term *reward* tends to evoke the idea of pleasure or hedonia, even if this is not intended by the author (Salamone & Correa, 2012).

Does DA Mediate Pleasure or Hedonia?

Results from Animal Studies

Despite its popularity, the idea that interference with DA systems causes “anhedonia” is highly controversial, and there is considerable evidence against it. Although sucrose consumption or preference is sometimes used as a measure of food-related hedonia (e.g., Johnson & Kenney, 2010), there are several reasons why consumption or preference measures per se are not reliable indices of the emotional state. For example, if sucrose consumption is impaired by a particular treatment, it may reflect changes in a number of different processes other than emotion, including oral motor function, approach to the drinking tube, or sensorimotor responsiveness (Muscat & Willner, 1989; Berridge, 2000, 2007; Sederholm, Johnson, Brodin, & Södersten, 2002; Salamone & Correa, 2002). In order to address these concerns, one of the tests that has become widely accepted as a measure hedonic reactivity to sweet solutions is the taste reactivity paradigm. Over the last several years, a substantial body of research from Berridge and colleagues has demonstrated that systemic administration of DA antagonists, whole forebrain DA depletions, or local depletions of nucleus accumbens DA fail to blunt appetitive taste reactivity for food (Berridge & Robinson, 1998, 2003; Berridge, 2007). Furthermore, manipulations that elevate extracellular DA, including knockdown of the DA transporter (Peciña, Cagniard, Berridge, Aldridge, & Zhuang, 2003) and microinjections of the stimulant drug amphetamine directly into nucleus accumbens (Smith, Berridge, & Aldridge, 2011), failed to enhance appetitive taste reactivity for sucrose. Although nucleus accumbens shell DA D2 receptors appeared to regulate aversive taste reactivity, and stimulation of DA D2 receptors in the brainstem suppressed sucrose consumption, neither population of receptors mediated the hedonic display of taste (Sederholm et al., 2002). These findings and others have led Berridge and Robinson (1998, 2003) to conclude that brain DA does not mediate “liking” (i.e., the hedonic reaction to food). Nevertheless, these authors have suggested that DA systems are involved in “wanting” (i.e., incentive motivation) of natural and drug rewards (see Berridge, 2007).

A superficial review of some articles in the DA literature may leave one with the impression that ventral striatal/nucleus accumbens DA is selectively involved in hedonic processes, appetitive motivation, and reinforcement-related learning, but not in aspects of aversive emotion or motivation. For example, it has been stated that increases in DA release are only associated

with appetitive stimuli, not aversive ones (e.g., Burgdorf & Panksepp, 2006). Nevertheless, such a suggestion is not supported by the literature. Neurochemical markers of accumbens DA transmission, such as extracellular levels of DA as measured by microdialysis, are elevated in response to a diverse variety of aversive conditions, including foot shock, tail shock, tail pinch, restraint stress, instrumental avoidance, conditioned aversive stimuli, anxiogenic drugs, and social defeat stress (Salamone, 1994, 1996; McCullough, Sokolowski, & Salamone, 1993; Tidey & Miczek, 1996; Datla, Ahier, Young, Gray, & Joseph, 2002; Young, 2004; Marinelli, Pascucci, Bernardi, Puglisi-Allegra, & Mercuri, 2005). Although the slow time resolution of microdialysis methods makes it difficult to establish specific relations between neurochemical changes and transient behavioral or environmental events, several investigators have used electrophysiological and voltammetric methods (i.e., electrochemical methods that detect transient changes in extracellular DA) to obtain markers of fast phasic DA activity. For many years, it was thought that activity of putative ventral tegmental DA neurons was not increased by aversive stimuli. However, Guaraci and Kapp (1999) showed that putative ventral tegmental DA neurons responded to the conditioned stimulus during Pavlovian fear conditioning, and subsequently, Anstrom and Woodward (2005) reported that virtually all putative ventral tegmental DA neurons from which they recorded showed increased activity during restraint stress. More recent studies have confirmed that the electrophysiological activity of putative or identified DA neurons is increased by aversive or stressful conditions (Brischoux, Chakraborty, Brierley, & Ungless, 2009; Matsumoto & Hikosaka, 2009; Bromberg-Martin, Matsumoto, & Hikosaka, 2010; Schulz, 2010; Lammel, Ion, Roeper, & Malenka, 2011). Although Roitman, Wheeler, Wightman, and Carelli (2008) reported that an aversive taste stimulus (quinine) decreased DA transients in nucleus accumbens as measured by voltammetry, Anstrom, Miczek, and Budygin (2009) observed that social defeat stress was accompanied by increases in fast phasic DA activity, as measured by both electrophysiology and voltammetry.

Although it often is stated that interference with DA transmission impairs “reward”-related learning, a substantial literature also implicates DA systems in the behavioral response to aversive stimuli or stressful conditions, and in aversive learning. These studies go back several decades (Salamone, 1994) and have continued up to more recent reports (Faure, Reynolds, Richard, & Berridge, 2008; Zweifel et al., 2011). Considerable evidence indicates that interference with DA transmission can impair the acquisition or performance of aversively motivated behavior. In fact, for many years, DA antagonists underwent preclinical screening for assessment of potential antipsychotic activity based partly on their ability to blunt avoidance behavior (Salamone, 1994). Accumbens DA depletions impair shock avoidance lever pressing (i.e., Sidman avoidance; McCullough et al., 1993). Systemic or intra-accumbens injections of DA antagonists

also disrupt the acquisition of place aversion and taste aversion (Acquas & Di Chiara, 1991; Fenu, Bassareo, & Di Chiara, 2001), as well as fear conditioning (Inoue, Izumi, Maki, Muraki, & Koyama, 2000; Pezze & Feldon, 2004). Zweifel et al. (2011) reported that knockout of *N*-methyl-D-aspartate (NMDA) receptors, which acts to reduce fast phasic DA release, impaired the acquisition of cue-dependent fear conditioning. Furthermore, an emerging body of work has demonstrated that rats showing greater response to conditioned cues (sign-trackers) display different patterns of dopaminergic adaptation to training than do animals that are more responsive to the primary reinforcer (goal trackers; Flagel, Watson, Robinson, & Akil, 2007). Interestingly, the rats that show greater Pavlovian conditioned approach to an appetitive stimulus, and show greater incentive conditioning to drug cues, also tend to show greater fear in response to cues predicting shock, and greater contextual fear conditioning (Morrow, Maren, & Robinson, 2011).

In summary, research from the animal literature does not indicate that mesolimbic DA shows increased activity solely in response to stimuli or conditions that are marked by positive hedonic valence. Furthermore, the involvement of DA in instrumental behavior, learning, or motivation is not unique to appetitively motivated tasks. Finally, there is considerable evidence that interference with DA transmission does not blunt hedonic reactivity to taste stimuli. Taken together, these findings sharply challenge the long-held belief that mesolimbic DA is a critical mediator of pleasure or hedonia.

Results from Human Studies

Several lines of evidence indicate that there are many problems with the idea that DA systems mediate pleasure (Barrett, 2006; Salamone et al., 2007). For example, patients with Parkinson's disease, who have a severe DA depletion, were reported not to have significant alterations in the perceived pleasantness of gustatory stimuli (Sienkiewicz-Jarosz et al., 2005). In an early article focusing on the role of DA in the hedonic reaction to drugs of abuse, Gunne, Anggard, and Jonsson (1972) reported that the euphoric effects of amphetamine could be blocked by DA antagonism. Nevertheless, considerable research over the last few years has challenged this notion. Gawin (1986) studied the effects of DA antagonism in cocaine users, and these patients actually reported continued euphoria from cocaine, as well as lengthened cocaine binges. Brauer and de Wit (1997) investigated the effects of the DA antagonist pimozide, and reported that this drug failed to blunt amphetamine-stimulated euphoria. Neither the typical antipsychotic (and DA D2 antagonist) haloperidol nor the atypical antipsychotic risperidone suppressed the positive self-reported effects of methamphetamine (Wachtel, Ortengren, & de Wit, 2002). Furthermore, the DA D1 antagonist ecopipam failed to attenuate the self-administration and subjective euphoria induced

by cocaine (Haney, Ward, Foltin, & Fischman, 2001; Nann-Vernotica, Donny, Bigelow, & Walsh, 2001). Leyton, Casey, Delaney, Kolivakis, and Benkelfat (2005) demonstrated that catecholamine depletion induced by feeding people a phenylalanine/tyrosine-free diet did not reduce cocaine self-administration or cocaine-induced self-reported euphoria. A recent article from the same laboratory described the ability of catecholamine synthesis inhibition to differentiate between different aspects of motivation and emotion in humans (Venugopalan et al., 2011). In this article, the investigators manipulated DA transmission by transiently inhibiting catecholamine synthesis with phenylalanine/tyrosine depletion, and access to cigarette smoking was used as a reinforcer. Inhibition of catecholamine synthesis did not attenuate self-reported craving for cigarettes, nor did it blunt smoking-induced hedonic responses. Nevertheless, it did lower progressive ratio break points for cigarette reinforcement (i.e., the number of operant responses in which the people would engage to obtain the cigarettes), indicating that people with reduced DA synthesis showed a reduced willingness to work for cigarettes.

Imaging methods have allowed for *in vivo* assessment of the responsiveness to appetitive and aversive stimuli in DA terminal areas in humans. Several studies have focused on emotional stimuli, and, as in the early animal research, a common view is that accumbens/ventral striatal activity as measured in imaging studies is closely associated with pleasure (e.g., Peterson, 2005; Keedwell, Andrew, Williams, Brammer, & Phillips, 2005; Sarchiapone et al., 2006). In fact, it is not clear whether the imaging response is greater in response to the primary motivational stimulus, to cues that predict the occurrence of that stimulus, or to the instrumental action. For example, Knutson, Fong, Adams, Varner, and Hommer (2001; Knutson, Fong, Bennett, Adams, & Hommer, 2003) reported that accumbens functional magnetic resonance imaging (fMRI) activation was evident in people performing a gambling task, but that the increased activity was associated with reward prediction or anticipation rather than presentation of the monetary reward per se. O'Doherty, Deichmann, Critchley, and Dolan (2002) observed that anticipation of glucose delivery was associated with increased fMRI activation in midbrain and striatal DA areas, but that these areas did not respond to glucose delivery. In addition, a recent imaging article indicated that doses of the DA precursor L-dihydroxyphenylalanine (L-dopa) that enhanced the striatal representation of appetitively motivated actions did not affect the neural representation of reinforcement value (Guitart-Masip et al., 2012). Evidence from imaging studies also indicates that the response of ventral striatum to anticipation of motivationally or emotionally significant stimuli is not unique to appetitive conditions. Jensen et al. (2003) showed that anticipation of an aversive cutaneous stimulus was associated with fMRI activation of ventral striatum.

Activation of accumbens fMRI responses was related to emotional intensity for both positive and aversive conditions (Phan et al., 2004).

Vietnam War veterans with posttraumatic stress disorder demonstrated increased blood flow in nucleus accumbens in response to the presentation of aversive stimuli (i.e., combat sounds; Liberzon et al., 1999). Aharon, Becerra, Chabris, and Borsook (2006) observed that distinct subregions of the accumbens undergo temporally dependent activation or inhibition of fMRI signals in response to a painful thermal stimulus, which may be related to the perception or anticipation of the stressor. Human imaging studies indicate that ventral striatal blood-oxygen-level-dependent (BOLD) responses, as measured by fMRI, are increased in response to prediction errors regardless of whether the stimulus predicted rewarding or aversive events (Jensen et al., 2007), and that aversive prediction errors were blocked by the DA antagonist haloperidol (Menon et al., 2007). Baliki, Geha, Fields, and Apkarian (2010) reported that in normal subjects, phasic BOLD responses occurred at both the onset and offset of a painful thermal stimulus. Levita et al. (2009) used fMRI to delineate brain response to the onset and offset of unpleasant and pleasant auditory stimuli in the absence of any learning or motor responses; they observed that increased nucleus accumbens activity was present for the onset of both pleasant and unpleasant stimuli. Delgado, Jou, and Phelps (2011) demonstrated that ventral striatal BOLD responses were increased during aversive conditioning to a primary aversive stimulus (shock) as well as monetary loss. Although most imaging studies do not deal directly with DA per se, Preussner, Champagne, Meaney, and Dagher (2004) used positron emission tomography (PET) measurements of *in vivo* raclopride displacement to assess DA release in humans, and observed that exposure to psychosocial stress increased markers of extracellular DA in the ventral striatum in a manner that was correlated with increased cortisol release.

To summarize, research with human subjects, like that with animals, also has failed to support the idea that DA systems, or the ventral striatum/nucleus accumbens, respond uniquely or selectively to pleasurable stimuli or conditions that are marked by positive hedonic valence. Furthermore, the preponderance of evidence indicates that interference with DA transmission in humans does not selectively affect self-reported pleasure or euphoria in response to primary motivational stimuli or drugs of abuse. Together with the animal studies, these findings provide a strong challenge to the hypothesis that mesolimbic DA or the ventral striatal region is a critical mediator of pleasure or hedonia.

DA Transmission as a Vital Contributor to Motivational Processes and an Ingredient in Emotional Processes

As reviewed earlier, DA transmission in the nucleus accumbens does not appear to be a specific marker of hedonic reactivity. Furthermore, evidence indicates that accumbens DA activity does not mediate primary motivation

or appetite for natural stimuli such as food. Although it is generally agreed that whole-forebrain DA depletions impair food intake, this effect is closely linked to depletions or antagonism of DA in the sensorimotor or motor-related areas of lateral or ventrolateral neostriatum, but not the nucleus accumbens (Koob, Riley, Smith, & Robbins, 1978; Salamone, Mahan, & Rogers, 1993). Baldo, Sadeghian, Basso, and Kelley (2002) reported that D1 and D2 antagonists injected into either core or shell subregions of nucleus accumbens at doses that suppressed locomotor activity failed to affect food intake. Moreover, the effects of DA antagonists or accumbens DA depletions on food-reinforced instrumental behavior differ substantially from the effects of appetite suppressant drugs (Salamone & Correa, 2002; Sink, Vemuri, Olszewska, Makriyannis, & Salamone, 2008), and from reinforcer devaluations such as prefeeding (Salamone et al., 1991; Aberman & Salamone 1999; Pardo et al., 2012). Furthermore, the DA antagonist flupenthixol did not affect the palatability of food reward or the increase in palatability induced by the upshift in motivational state produced by increased food deprivation (Wassum, Ostlund, Balleine, & Maidment, 2011). Moreover, the long-held view about DA as a critical neural mechanism underlying addiction is being revised, and DA is now seen as being more related to its involvement in the initial reinforcing characteristics of drugs. It has become more common to view addiction in terms of neostriatal habit-formation mechanisms built on extensive drug taking, which can be relatively independent of instrumental reinforcement contingencies or the initial motivational characteristics of drug reinforcers (Belin, Jonkman, Dickinson, Robbins, & Everitt, 2009). These emerging views about the neural basis of drug addiction, and its potential treatment, have moved well beyond the original concepts offered by the DA hypothesis of "reward."

So, if nucleus accumbens DA does not mediate hedonic responses to stimuli such as food or drugs of abuse, and does not mediate primary motivation or appetite for food, then what functions does it perform? A thorough discussion of this topic is beyond the scope of this chapter (see Salamone & Correa, 2012), but we provide a brief summary. A significant body of evidence indicates that accumbens DA depletions or antagonism leave core aspects of food-induced hedonia, appetite, or primary food motivation intact but do affect critical features of the instrumental (i.e., food-seeking) behavior. Nucleus accumbens DA is particularly important for mediating motivational aspects of motivation (i.e., behavioral activation; Koob et al., 1978; Robbins & Koob, 1980; Salamone, 1988, 1991; Salamone, Correa, Mingote, & Weber, 2005; Salamone et al., 2007; Calaminus & Hauber, 2007; Lex & Hauber, 2010), exertion of effort during instrumental behavior (Salamone, Cousins, & Bucher, 1994; Salamone, Correa, Nunes, Randall, & Pardo, 2012; Salamone et al., 2007; Treadway et al., 2012), Pavlovian responsiveness to instrumental transfer and to conditioned stimuli (Wyvell & Berridge, 2000; Everitt & Robbins, 2005; Lex

& Hauber, 2008), incentive salience (Berridge, 2007); flexible approach behavior (Nicola, 2010), energy expenditure and regulation (Salamone, 1987; Beeler, Frazier, & Zhuang, 2012), and exploitation of reward learning (Beeler, Daw, Frazier, & Zhuang, 2010). Putting all these related ideas together, it has been suggested that nucleus accumbens DA helps organisms overcome the “psychological distance” that separates them from significant stimuli (Salamone & Correa, 2012). In other words, accumbens DA transmission facilitates the process of enabling organisms to surmount various obstacles (e.g., physical distance, time, probability, instrumental requirements) that separate them from these motivations or events. These functions obviously represent critical aspects of motivation, but they are quite different from maintaining that DA is some kind of “pleasure chemical” or that DA systems mediate “reward” or hedonia.

In view of the clear evidence linking DA transmission to aspects of motivation, what does this say about dopaminergic involvement in emotion? Is DA irrelevant as an ingredient in emotional states? Not necessarily. Burgdorf and Panksepp (2006) suggested that ventral striatal mechanisms are not related to “pleasure” or “consummatory reward” in the traditional sense, but instead are involved in anticipatory or appetitive energizing effects of stimuli. More recently, Panksepp (2011) has described how emotional networks in the brain are interwoven with motivational systems involved in patterns of behavior such as seeking, rage, or panic. Thus, it is possible that mesolimbic DA, while acting as a vital mediator of several important aspects of motivation, also contributes to the emotions experienced during seeking or avoidance behavior. In addition, it is possible that DA participates in the intensity or arousal dimension of emotions, as opposed to the valence dimension (Russell & Barrett, 1999; Phan et al., 2004). Finally, DA transmission in the nucleus accumbens may generate internal stimuli consistent with feelings of self-reported energy or efficacy (i.e., “I can obtain this” or “I can avoid this”; Salamone, 1991; Nesse & Berridge, 1997). Examples of this include the omnipotence and power that cocaine addicts report as the main feelings the drug produces (Sherer, Kumor, & Jaffe, 1989), and the concept of self-perceived fitness (Newlin, 2002). These speculations all point to a potential role for nucleus accumbens DA as an ingredient in the emotional stew, albeit one that may affect taste quite differently depending on the rest of the ingredients.

A rejection of the idea that mesolimbic DA mediates hedonia or euphoria also can help to reshape concepts about the involvement of this system in psychopathology, and shed light on the nature of emotional disruptions seen across various disorders. For example, it no longer seems tenable to maintain that reduced DA transmission is the fundamental cause of anhedonia (in terms of an inability to experience pleasure) in depression. Indeed, there are several problems with this. As reviewed by Treadway and Zald (2011), multiple studies have shown that the hedonic responses of depressed

patients to the direct experience of pleasurable stimuli appear to be relatively intact. Instead, many depressed people have more clear difficulties with pursuit of motivational stimuli, exertion of effort, and motivational anticipation. In fact, it can be argued that in many instances depressed patients are mislabeled as anhedonic, when their more fundamental pathologies may be related to psychomotor retardation, anergia or motivational apathy. Considerable evidence indicates that DA systems are involved in these motivational symptoms of depression (Salamone, Correa, Mingote, Weber, & Farrar, 2006; Salamone et al., 2007; Treadway & Zald, 2011). Thus, mesolimbic DA and related brain circuits could be contributing substantially to the symptomatology of depression, but in a manner quite different from that outlined by the DA hypothesis of "reward."

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